REMARKS

Applicants appreciate the allowed claims 1-16. Reconsideration of the rejections of claims 17-20, 22-23 and 27-30 are respectfully requested in view of the following comments.

On page 6 of the office action, the examiner has commented that the difference between the prior art of Vincent et al. and the instant invention is that the applicants are claiming a pharmaceutical composition comprising the hydrated form of a pharmaceutically acceptable salt of perindopril, whereas the prior art teaches a pharmaceutical composition comprising a pharmaceutically acceptable salt of perindopril.

The examiner continues that Vincent et al. teaches a pharmaceutical composition comprising the claimed compound and a pharmaceutically acceptable carrier or excipient. According to the examiner, water meets the limitation of pharmaceutical acceptable carrier and therefore a hydrated form of pharmaceutically acceptable salt of perindopril would be present in the pharmaceutical composition.

Applicants submit that the examiner has attached the wrong construction to the term "hydrated" in the context of the present application. More specifically, it would be perfectly clear to the skilled person that the "hydrated form" of a pharmaceutically acceptable salt of perindopril refers to a specific crystallisation state of the pharmaceutically acceptable salt of perindopril. In this regard, enclosed is an extract from "Polymorphism in the Pharmaceutical Industry"(edited by-Rolf-Hilfiker) which explains that crystallisation from solutions may yield crystals of a molecular adduct, which contain two or more chemical components together in the same crystalline lattice. Solvates are common molecular adducts, and a hydrate is a special case of a solvate, when the incorporated solvent is water. The presence of solvent molecules in the crystal lattice influences the intermolecular interactions and confers unique physical properties to each solvate. Thus, a hydrate, in the context of the present application, is a particular solid phase of a chemical substance having a characteristic value for each of its physicochemical properties. For example, the unique XRPD patent for perindopril t-butylamine monohydrate is given in table 1 of the present application.

In the context of the present invention, "hydrated" does not, contrary to the examiner's assertion, simply refer to an aqueous solution of a pharmaceutically acceptable salt of perindopril.

The examiner has commented that the applicants have failed to show any unexpected results that occur when using the hydrated form of perindopril or any differences when comparing perindopril with the hydrated form of perindopril in the original disclosure. Although not specifically mentioned in the present application, the applicants have found that the hydrated salt is non-hygroscopic, has better flow characteristics and better compressibility compared to non-hydrated salts of perindopril.

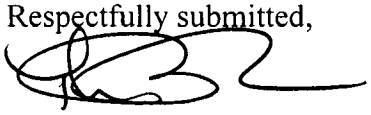
Therefore, applicants respectfully submit that the mere selection of an excipient, such as water, does not form a "hydrated" form of the drug perindopril. Accordingly, withdrawal of the associated rejection based on Vincent is requested.

Reconsideration of the rejection of claim 30 under 35 USC 112, first paragraph is respectfully requested. The examiner is referred specifically to the specification, page 7 following the Table through page 9, first full paragraph. The use of the claimed hydrated salt, including routes of administration, form of dosage, and ACE inhibitor effect are all disclosed therein. The authority cited by the examiner is not relevant to the instant rejection. Applicants are not claiming use of a genus of compounds, but use of a specific form of a single compound and described in the specification how to formulate and administer said compound to inhibit ACE. Contrary to the assertions, applicants do not claim treating specific diseases, such as Alzheimers. Applicant's claim 30 is specific to a method of inhibiting ACE and the examiner's speculation as to what diseases can benefit from ACE inhibitors are pure speculation on the examiner's part. Therefore, applicants need not respond to treating diseases, such as Alzheimers, or any other disease treatment, not claimed. Withdrawal of the rejection is therefore appropriate.

An amended Abstract deleting the word "said" is attached.

If any fees are necessary to make this application timely and/or complete, such fees may be deducted from Deposit Account No. 19-4375.

Respectfully submitted,



TPP/pgw
Attorney Docket No.: TPP 31767

Thomas P. Pavelko
Registration No. 31,689

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N.W., Suite 850
Washington, D.C. 20036
Telephone: (202) 785-0100
Facsimile: (202) 408-5200 or (202) 725-0200
Date: August 3, 2007

ATTACHMENT (as noted) - Polymorphism in the Pharmaceutical Industry

cluster that exhibits the fastest growth rate as a result of its lowest free energy barrier to nucleation. Although the stable polymorph A may have the greater thermodynamic drive to crystallize; polymorph B may nucleate first due to its higher nucleation rate. However, the nature of polymorph that eventually crystallizes is determined by the combination of the relative nucleation rates and the relative crystal growth rates of the polymorphs [46].

2.8
Introduction to Solvates and Hydrates

Often, crystallization from solution yields crystals of a molecular adduct, which contains two or more chemical components together in the same crystalline lattice. Solvates and hydrates are common molecular adducts. Haleblian [5] defined a solvate as a crystalline molecular compound in which molecules of the solvent of crystallization are incorporated into the host lattice, consisting of unsolvated molecules. A hydrate is a special case of a solvate, when the incorporated solvent is water. The presence of solvent molecules in the crystal lattice influences the intermolecular interactions and confers unique physical properties to each solvate. Therefore, a solvate has its own characteristic values of internal energy, enthalpy, entropy, Gibbs free energy, and thermodynamic activity. Consequently, the solubility and dissolution rate of a solvate differ from those of the corresponding unsolvated phase and can result in differences in bioavailability of drugs. In general, a solvate will have a lower solubility in the solvent, from which it crystallizes as a solvate, than the unsolvated phase(s) [63]. Subsequent sections will focus on hydrates, because they are more common than solvates of organic solvents [64]. Nevertheless, the concepts developed below are applicable to any solvate system.

2.8.1
Thermodynamics of Hydrates

On the basis of the water uptake behavior at different water activities, hydrates can be classified as either stoichiometric or non-stoichiometric. Stoichiometric hydrates for which the mole ratio of water/host is constant (Fig. 2.7) have a defined stoichiometry over a range of water activities. Examples of important stoichiometric pharmaceutical hydrates include ampicilline trihydrate [65] and theophylline monohydrate [66]. However, for non-stoichiometric hydrates (Fig. 2.8, below), the mole ratio, water/host, may vary continuously as a function of water activity.

Figure 2.7 shows a hydrate system that forms two stoichiometric hydrates with m and n moles of water ($n > m$), respectively. Formation of m-hydrate from the anhydrous phase can be expressed as:

$$D(solid) + mH_2O \rightleftharpoons D.mH_2O(solid)$$

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ne is the volume
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